

Monographs on drugs which are frequently analyzed in therapeutic drug monitoring

Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

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Abstract

In addition to the monographs which have been published in the past 7 years by the working group “Drug Monitoring” of the Swiss Society of Clinical Chemistry (SSCC) [1–6], new monographs have been written. The data presented in these monographs provide an overview of the information which is important for the request and interpretation of the results. Therefore, laboratory health professionals and the receivers of the reports are the targeted readers. In this series, antiretroviral drugs are presented for which drug concentrations are regularly determined (protease inhibitors, non-nucleoside reverse transcriptase inhibitors). To date, no clear evidence has been established that therapeutic drug monitoring of these drugs increases the success of the antiretroviral therapy. Nevertheless, many cases have demonstrated that the therapy can be guided with much more confidence and with good success if the drug concentrations are determined, especially if the patient has a combination therapy with many pharmacokinetically interfering compounds. First, information is given about pharmacology and pharmacokinetics of these drugs, such as protein binding, metabolic pathways with specific enzymes involved, elimination half-life time, elimination route(s) of the

parent drug, as well as therapeutic and toxic concentrations. Moreover, indications for therapeutic drug monitoring are listed with important preanalytical information (time point of blood sampling and time to steady state since beginning or after change of posology). Furthermore, the stability of the drug and its metabolite(s) after blood sampling are described. For readers with a specific interest, references to important publications are given. The number of monographs will be further enlarged. The updated files are presented on the homepage of the SSCC (www.sccc.ch). We hope that these monographs are helpful for the better handling of therapeutic drug monitoring and we are looking forward to receiving comments from the readers.

Keywords: atazanavir; darunavir; efavirenz; fosamprenavir; lopinavir; nelfinavir; nevirapine; ritonavir; saquinavir; tipranavir.

Zusammenfassung

Ergänzend zu den in den letzten 7 Jahren publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1–6], sind weitere Monographien erstellt worden. Wiederum sollen diese Monographien dem Labormediziner bzw. dem Empfänger der Befunde eine Übersicht über die wichtigsten Informationen geben, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind. In dieser Serie werden diejenigen antiretroviralen Medikamente (Proteaseinhibitoren, nicht nukleotid Inhibitoren der reversen Transkriptase) beschrieben, bei denen regelmässige Messungen der Konzentrationen durchgeführt werden. Obwohl bis heute keine klare Evidenz vorhanden ist, dass ein Therapeutic Drug Monitoring den Therapieerfolg verbessert, zeigt sich doch in vielen Einzelfällen, dass vor allem bei Kombinationstherapien, auch mit Medikamenten aus anderen Arzneimittelklassen, die Therapie durch das Messen der Medikamentenkonzentrationen und die anschliessende Dosisanpassung sicherer und mit gutem therapeutischem Erfolg gestaltet werden kann. Die einzelnen Monographien beinhalten einerseits Angaben zu klinisch-pharmakologischen Daten wie zum Beispiel den

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Proteinbindungen, Metabolisierungswegen und den daran beteiligten Enzymen, Halbwertszeiten und Eliminationswege der Muttersubstanz, sowie Informationen zu therapeutischen bzw. toxischen Bereichen. Andererseits werden bei jeder Substanz die Indikationen für das Therapeutic Drug Monitoring aufgelistet und wichtige Angaben zur Präanalytik gemacht (Zeitpunkt der Blutentnahme und Zeitpunkt des Erreichens einer steady-state-Situation nach einer Dosisänderung). Ausserdem werden Angaben über die Stabilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gemacht. Für die interessierten Leser sind die verwendeten Referenzen

als Zitate aufgeführt. Die Zahl der Monographien wird weiterhin ergänzt. Die aktuellsten Versionen der Monographien sind auf der Homepage der SGKC abrufbar (www.ssgc.ch). Wir hoffen, dass diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Atazanavir; Darunavir; Efavirenz; Fosamprenavir; Lopinavir; Nelfinavir; Nevirapine; Ritonavir; Saquinavir; Tipranavir.

Atazanavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Reyataz®
- Conversion factors: $\text{mg/L} \times 1.42 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.70 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: ~86%
- Elimination half-life: 6–7 h; 12 h with ritonavir
- Volume of distribution: 1.2 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s)? None
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4 > CYP1A2 > CYP2C9
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: >0.14 mg/L (>0.20 $\mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 week frozen at –20°C

Remarks

Target values only as indications, not really defined values.

References

- Arzneimittelkompendium Schweiz, www.kompendium.ch.
- Baselt RC. Disposition of toxic drugs and chemicals in man. 8th ed. Foster City, CA: Biomedical Publications, 2009.
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Darunavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Prezista®
- Conversion factors: $\text{mg/L} \times 1.83 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.55 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: ~95%
- Elimination half-life: 12–15 h (with ritonavir)
- Volume of distribution: $1.3 \pm 1 \text{ L/kg}$
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s)? None
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: $>3.52 \text{ mg/L}$ ($>6.40 \mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 week frozen at -20°C

Remarks

Target values only as indications, not really defined values.

References

- Arzneimittelkompendium Schweiz, www.kompendium.ch.
- Baselt RC. Disposition of toxic drugs and chemicals in man. 8th ed. Foster City, CA: Biomedical Publications, 2009.
- Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit* 2011;33:265–74.
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Efavirenz

General

- Class of the drug: Non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Synonym(s):
- Common trade name(s) in Germany: Sustiva®, Atripla®
- Conversion factors: $\text{mg/L} \times 3.17 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.31 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: >99%
- Elimination half-life: 52–78 h (single dose); 40–60 h (multiple doses)
- Volume of distribution: $1.05 \pm 0.84 \text{ L/kg}$
- Metabolism:
 - Main metabolic pathways: CYP3A4, CYP2B6
 - Active metabolite(s)? None
 - Inhibitor or inducer of the cytochrome P450 system? Inducer of CYP3A4, CYP2B6
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination: Mainly hepatic
- Typical therapeutic range: >0.10 mg/L (>0.32 nmol/L) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~12 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 week frozen at -20°C

Remarks

Target values only as indications, not really defined values.
Efavirenz induces its own metabolism.

References

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Fosamprenavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Telzir®
- Conversion factors: $\text{mg/L} \times 1.98 = \mu\text{mol/L}$ (amprenavir)
 $\mu\text{mol/L} \times 0.50 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: >90%
- Elimination half-life: 7–10 h (amprenavir); 15–23 h (amprenavir with ritonavir)
- Volume of distribution: 1.2 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s)? Amprenavir
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: 0.40 mg/L (>0.80 $\mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days (5 days with ritonavir)
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 week frozen at -20°C

Remarks

Fosamprenavir is rapidly and extensively converted to amprenavir.
Target values only as indications, not really defined values.

References

- Arzneimittelkompendium Schweiz, www.kompendium.ch.
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Lopinavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Kaletra®
- Conversion factors: $\text{mg/L} \times 1.59 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.63 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: >99%
- Elimination half-life: 5 h
- Volume of distribution: 0.5 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s): 4-oxo- and 4-hydroxy-lopinavir (low concentrations)
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: >0.10 mg/L (>0.16 $\mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 week frozen at -20°C

Remarks

Target values only as indications, not really defined values.
Galenic form contains both lopinavir and ritonavir.

References

- Arzneimittelkompendium Schweiz, www.kompendium.ch.
- Baselt RC. Disposition of toxic drugs and chemicals in man, 8th ed. Foster City, CA: Biomedical Publications, 2009.
- Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit* 2011;33:265–74.
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Nelfinavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Viracept®
- Conversion factors: $\text{mg/L} \times 1.76 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.57 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: >98%
- Elimination half-life: 3.5–5 h
- Volume of distribution: 2–7 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4, CYP2C19
 - Active metabolite(s)? M8 (oxidizes metabolite, low concentrations)
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4 and CYP2B6
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: >1.40 mg/L (>2.46 $\mu\text{mol/L}$) (morning)
>0.80 mg/L (>1.41 $\mu\text{mol/L}$) (evening)
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~2 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 month frozen at -20°C

Remarks

The pharmacokinetics of nelfinavir is displaying significant diurnal variation. Target values only as indications, not really defined values.

References

- Arzneimittelkompendium Schweiz, www.kompendium.ch.
- Baselt RC. Disposition of toxic drugs and chemicals in man. 8th ed. Foster City, CA: Biomedical Publications, 2009.
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Nevirapine

General

- Class of the drug: Non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Synonym(s):
- Common trade name(s) in Germany: Viramune®
- Conversion factors: $\text{mg/L} \times 3.76 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.27 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: 61%
- Elimination half-life: 45 h (single dose); 25–30 h (multiple doses)
- Volume of distribution: 1.2–1.5 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4, CYP2B6
 - Active metabolite(s)? Not known
 - Inhibitor or inducer of the cytochrome P450 system? Inducer of CYP3A4, CYP2B6
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: >3.5 mg/L (>13.2 $\mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~5 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 month frozen at -20°C

Remarks

Target values only as indications, not really defined values.
Nevirapine induces its own metabolism.

References

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Ritonavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Norvir®
- Conversion factors: $\text{mg/L} \times 1.39 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.719 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: 98–99%
- Elimination half-life: 3–5 h
- Volume of distribution: 0.3–0.6 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4, CYP2D6
 - Active metabolite(s): M2 (low concentrations)
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4 > CYP2D6 > CYP2C9; irreversible (suicide) inhibition of CYP3A4
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: >2.1 mg/L (>2.92 $\mu\text{mol/L}$) if administered as the only protease inhibitor or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 month frozen at -20°C

Remarks

Ritonavir is usually only used in low doses as inhibitor of CYP3A4. Target values only as indications, not really defined values.

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Saquinavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Invirase®
- Conversion factors: $\text{mg/L} \times 1.49 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.67 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: 98%
- Elimination half-life: 1–2 h
- Volume of distribution: 7–13 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s)? None
 - Inhibitor or inducer of the cytochrome P450 system? Inhibitor of CYP3A4
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: $>0.10 \text{ mg/L}$ ($>0.15 \mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 month frozen at -20°C

Remarks

Target values only as indications, not really defined values.

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Tipranavir

General

- Class of the drug: Protease inhibitor (PI)
- Synonym(s):
- Common trade name(s) in Germany: Aptivus®
- Conversion factors: $\text{mg/L} \times 1.66 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.60 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM: Individual dose adaptation, compliance verification, side effects, intoxication
- Protein binding: 99.9%
- Elimination half-life: ~6 h
- Volume of distribution: 0.1–0.2 L/kg
- Metabolism:
 - Main metabolic pathways: CYP3A4
 - Active metabolite(s)? None
 - Inhibitor or inducer of the cytochrome P450 system? Not known
 - Other significant pharmacokinetic interactions: Substrate for P-glycoprotein
- Elimination of parent drug: Mainly hepatic
- Typical therapeutic range: >20.5 mg/L (>34.0 $\mu\text{mol/L}$) or Bayesian approach
- Potentially toxic concentration: Not known

Pre-analytics

- Time to steady state since beginning of treatment or change of posology: ~3 days
- Time for blood sampling: Before next dose at steady state
- Type(s) of sample: Serum or plasma
- Stability: At least 1 month frozen at -20°C

Remarks

Target values only as indications, not really defined values.

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

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